The Preparation and Sterilization of Ophthalmic Solutions

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SUMMARY

Ophthalmic solutions should be prepared and preserved according to whether they are to be used in surgical procedures, in the clinic or office, or by the patient at home.

There is an optimum pH level at which the solutions of individual drugs should be buffered in order to obtain the maximum efficiency and stability.

Deterioration of the drugs used is greatly diminished when they are dispensed at the proper pH.

Quaternary ammonium chloride solutions in proper strength have been shown to be adequate for the preservation of ophthalmic solutions.

EXCELLENT work has been done in recent years to clarify the factors which influence the irritation, stability, absorption and sterility of ophthalmic medications. Most of the published reports of this work have appeared in pharmacologic journals, except for those on studies of individual drugs, which have appeared in the ophthamologic literature.

The development of more effective antiseptics has aided materially in the preservation of ophthalmic solutions used in surgical procedures and by patients. It has been found that there is a good deal of conflict in the ophthalmic literature concerning both the preservation and sterilization of these medications. A number of articles state that it is permissible to autoclave surgical solutions after they are prepared. These reports have neglected to indicate the probable deterioration which occurs in many solutions after the application of heat. It is felt that a review of some of the more recent excellent work on the preparation and sterilization of these solutions will be valuable to ophthalmologists.

Ophthalmic solutions should be prepared and preserved according to whether they are to be used: (1) In surgical procedures; (2) in the clinic or office; (3) at home.

Those solutions which are to be used in the office, at home, and by the patient, may be prepared as indicated later in this presentation. It is considered satisfactory to add a preservative, since the medication is used for a very short period. Surgical solutions should be prepared with great care, and necessary precautions should be taken to insure their sterility.

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IMPORTANT FACTORS IN PREPARING SOLUTIONS

The ideal ophthalmic solution should be sterile, non-irritating, stable, and active. The effect of individual drugs upon the eye is influenced by dilution by the tears, precipitation of the basic drug or a salt by tears and mucus, the reaction of the tissues and tears, the reaction of the drug, and by the concentration and frequency of use of the drug. The last two factors are considered as most important, since they are the qualities which can be altered most easily.

The *reaction* of the medication used is very important and numerous articles have been presented to show the influence the pH has on optimum absorption of drugs. However, it is not always possible to adjust the pH of a solution so that it will be absorbed properly. Its chemical stability and the irritation caused by contact with the eye may require alteration of the pH to a slightly less desirable level. Therefore, it must be accepted that there is an optimum pH level at which the solutions of individual drugs should be buffered in order to obtain the maximum efficiency and stability. It has been stated that ophthalmic solutions should be buffered to have a pH equal to that of the tears. This statement should be modified when one must consider the stability of the solution and the equilibrium constant of the free alkaloidal base. It has been shown that the physiologic effect of aqueous solutions of acid salts of active bases is related to the concentration of free base, and not to that of the ionized salt.[5] The irritation produced by most of these drugs is correlated with the concentration of the free base and can be controlled by lowering the pH of the solution.

The *stability* of solutions is especially important, since Blok[2] found a 44 per cent decomposition of 0.5 per cent atropine solution and 89 per cent decomposition of a 1 per cent homatropine solution in one month when they were dispensed at pH 8.3. Deterioration was less than 20 per cent when they were dispensed at pH 6.8. In general, slightly acid solutions of ophthalmic drugs are more stable and effective. If they are too acid, the free base is quite irritating. Other medications may be used at a higher pH because their bases are less irritating.

An additional consideration in adjusting the reaction is the relation between the pH of the solution and absorption by the eye. Fischer[4] showed that absorption of a 1 per cent atropine solution at pH 4.0 is only a third as great as it is at pH 7.5. A change in pH from 4.0 to 7.5 decreased the absorption of 0.5 per cent pilocarpine by 50 per cent. It has also been shown that changing the pH of 1 per cent cocaine solution from 3.2 to 8.7 increased its absorption sevenfold.

Wetting agents, which decrease the interfacial tension between air and liquids, and make the contact between solutions and membranes more intimate, promote greater absorption of many drugs. Carbaminoylcholine chloride, which is poorly absorbed in aqueous solution by the cornea, provides a good example. The addition of a wetting agent results in more constant and dependable absorption of the drug.

Osmotic pressure need not be taken into consideration in the preparation of most ophthalmic drugs. The tears are isotonic with a 0.9 per cent solution of sodium chloride. The eye, however, tolerates solutions having varying osmotic pressures (0.5 to 2 per cent).[8] A few drops of medication introduced into the conjunctival sac have a very transitory effect on the osmotic pressure.

BUFFER SOLUTIONS

Before proceeding to discuss the preparation of various solutions it is necessary to say a few words about buffer solutions. Buffers are certain salts which, when dissolved in water, resist a change in pH on the addition of a small amount of acid or base. The salts of weak acids, such as phosphoric acid and acetic acid, are called buffer salts. The same applies to the salts of weak bases. The addition of a relatively large amount of buffer salt in proportion to the amount of acid or base causes a fractional decrease of buffer ion. Buffer ion unites with H-ion to form the slightly dissociated acid corresponding to the buffer salt employed. The decrease in buffer salt is so slight that the H-ion concentration is fairly constant. Gifford stated that the addition of drugs to buffers does not modify their reaction more than pH 0.2. Hind and Goyan[9] have emphasized that different buffer systems have different capacities. Their capacity depends on the concentration and pH range of the system used. The Gifford buffer system has a high buffer capacity and should be used in the range pH 8-10. Below this range it has a tendency to become more alkaline on standing, due to liberation of carbon dioxide.

The most satisfactory borate buffer is that of Palitzsch, as modified by Goyan, Enright and Wells.[6] It is stable and has a buffer range between pH 8 and 10.

Sorensen's phosphate buffer system has a wide and practical usage. It is the one which is most commonly used in the University of California Hospital pharmacy. This system has a buffer range of pH 5.8 to 8. It is incompatible with zinc salts. It controls the pH of many ophthalmic drugs at the isohydric point of the tears.

PREPARATION OF VARIOUS SOLUTIONS

Atropine, homatropine, pilocarpine, eucatropine, and scopolamine should be dispensed in a phosphate buffer solution at pH 6.8. Hind and Goyan found only 10 to 20 per cent loss in activity of these drugs after 30 days. These drugs are made up in a solution of the desired strength, and quaternary ammonium chloride (Zephiran®, Phemerol®) is added so that the final solution contains a 1:10,000 concentration of this antiseptic.

Cocaine, pontocaine, procaine, and zinc should be dispensed in a weak boric acid solution at pH 5. Quaternary ammonium chloride is added to 1:10,000 strength. Boric acid is used so that when the drops come in contact with the tears they are buffered to about pH 5.0. Eserine solutions decompose by hydrolysis and oxidation. The oxidation products maintain the therapeutic activity of eserine but become irritating. If the pH of eserine is maintained at around 5 it is less irritating and more stable. Eserine solutions are prepared in the desired strength with boric acid. Sodium sulfite 0.1 per cent and phenyl mercuric nitrate to 1:100,000 concentration are added. Sodium sulfite is added as anti-oxidant.[9] Zinc salts are soluble and must be maintained below a pH of 6. Above this pH they form basic complexes of zinc, reducing the zinc ion concentration. The zinc salt is made up to desired strength in 2 per cent boric solution and preserved with quaternary ammonium chloride.

The sulfa drugs are precipitated at a pH below 8.2. They may be buffered with a borate buffer to pH 8.6 and preserved with quaternary ammonium chloride. Penicillin is unstable in the range below pH 4.8 and above pH 7.9. A phosphate buffer may be used to buffer the solutions at 6.5.

Florescein,® soluble, is stable but extremely liable to contamination by certain Gram-negative bacteria. The solution should be made up to desired strength containing 1:10,000 quaternary ammonium chloride. If this drug is made up in a borate buffer the final pH is 8.4. A precipitate forms on addition of the preservative but this incompatibility does not affect the usage or action of the drug. There is good evidence that this preservative is effective in preventing contamination of solutions used in office and clinic, provided the solutions are not kept too long. Solutions used in operations, however, should be autoclaved to insure sterility.

STERILIZATION

The most desirable method of maintaining sterility of ophthalmic solutions is by the addition of an inert, non-irritating, bactericidal and fungicidal agent which is compatible with the drug in use. One must strike a mean between that which is ideal and that which is practical. The only real way to have sterile solutions is to prepare them in ampules

which may be sterilized in the autoclave. This method is costly, time-consuming, and wasteful, for there is always some deterioration and a portion of the solution remains in the ampule after use. Another method is to have the solutions properly prepared and placed in 20 cc. sterile rubber-capped vials.[7] The solutions may be withdrawn into a hypodermic syringe and used as needed. The objection to this method is the deterioration which occurs on standing. The third and most commonly used system is to have the solutions in sterile bottles with screw tops. The required amount of solution is withdrawn with a sterile dropper. After the first usage the stock bottle should be considered unsterile. Cocaine solutions are partially self-sterilizing, but if they are to be used in connection with operations they should be placed in rubber-capped vials and sterilized by boiling for 30 minutes in a water bath. The water bath temperature should not be below 60° C. and not over 80° C. Solutions used in the office, clinic, or home should be prepared in as sterile a manner as possible and a preservative added. For office and clinic use the bottles should be covered with a screw top. At the treatment table sufficient drops for each patient may be withdrawn in small sterile droppers. A dropper should never be reinserted in a bottle, and droppers used for atropine, scopolamine, and homatropine should be segregated from those used for other solutions.

The most desirable method of maintaining sterility in ophthalmic solutions is to add quaternary ammonium chloride solution. Skolant[11] has shown that it maintains the sterility of solutions which are used in surgical procedures. This antiseptic is satisfactory provided it is not used in too high a concentration. Swan has shown that 1:1,000 Zephiran® chloride is very irritating to the human conjunctiva, and produces edema and desquamation. A 1:3,500 solution produced some conjunctival and corneal changes which were reversible.[10] It is probably safer to use a 1:10,000 solution for preservation of ophthalmic solutions. Eserine and the Gifford buffers are incompatibile with this antiseptic. In addition to being a good sterilizing agent, this drug also acts as a wetting agent, aiding absorption of the drug.

All chemicals used to prepare ophthalmic solutions should be as chemically pure as possible. All vials, bottles, and caps should be washed with soap and water, thoroughly rinsed and autoclaved. Graduates, stirring rods, and containers should be sterile. Bottles used in office and clinics should be amber-colored to prevent deterioration of the drug. Drops for patients with glaucoma should be prescribed in small amounts, placed in amber bottles, and replaced at least monthly.

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Discussion by MAURICE W. NUGENT, M.D., *Los Angeles*

First I would like to recommend the two chapters in Remington's "Practice of Pharmacy" (9th Edition) on isotonic solutions and collyria. This book is practical, well written and full of excellent reference. It is just as necessary for pharmacists to recognize this problem as it is for ophthalmologists in order that prescriptions be filled according to recommended procedure. The basic principle must be set down for all concerned to follow.

All eye solutions must have clarity and be free of foreign particles and precipitates. An all-glass sintered-disc buckner funnel is excellent for this purpose. This filter will also remove bacteria and is one way of achieving bacterial sterilization. The funnel must be sterilized, of course. This funnel also has a choice of porosity.

Dr. Hogan has covered the buffering of eye solutions and I have nothing significant to add other than to recommend Gifford's buffer solution and to state these are approximately isotonic with lacrimal fluid and therefore serve a double purpose. The other buffer tables which Dr. Hogan mentioned must also be recommended, but it seems that pharmacists are much better acquainted with Gifford's buffer solutions, and consequently I for one feel more secure using these.

Preservatives are also a necessity because of refrigeration not being practical. Zephiran® or Phemerol® have proven themselves to be excellent and should be used wherever indicated.

Another point to be recommended is the use of multiple droppers, rather than the dropper bottle, for the obvious reason of contamination. It is most wise to keep only small quantities of medication on the treatment table and to discard these and re-sterilize the bottles at the beginning of each week. Medications used in the surgery should be dispensed in individual dosage ampules despite the extra cost.